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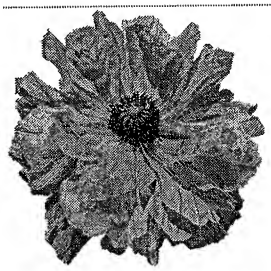

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Therapeutic Advances in the Treatment of Glioblastoma: Rationale and Potential Role of Targeted Agents

David A. Reardon and Patrick Y. Wen

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Therapeutic Advances in the Treatment of Glioblastoma: Rationale and Potential Role of Targeted Agents

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Key Words. Angiogenesis inhibitors • Glioblastoma multiforme • Targeted therapy • Tyrosine kinase inhibitors

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the genetic alterations frequently observed in GBM tumors as well as the cell signal transduction pathways that are aberrantly activated in these tumors.
2. Discuss the clinical benefit recently associated with temozolomide chemotherapy for patients with GBM.
3. Identify mediators of signal transduction pathways that are attractive targets of novel therapeutics in GBM patients.
4. Understand the potential benefit associated with regionally administered therapies for GBM patients as a means to overcome drug delivery limitations into the central nervous system caused by the blood–brain barrier.
5. Describe the rationale for combination regimens incorporating novel targeted agents for GBM patients.

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ABSTRACT

Despite advances in standard therapy, including surgical resection followed by radiation and chemotherapy, the prognosis for patients with glioblastoma multiforme (GBM) remains poor. Unfortunately, most patients die within 2 years of diagnosis of their disease. Molecular abnormalities vary among individual patients and also within each tumor. Indeed, one of the distinguishing features of GBM is its marked genetic heterogeneity. Nonetheless, recent developments in the field of tumor biology have elucidated signaling pathways and genes involved in the development of GBM, and several novel agents that target these signaling pathways are being developed. As new details on the genetic characteristics of this disease become available, innovative treatment regimens, including a variety of traditional treatment modalities such as surgery, radiation, and cytotoxic chemotherapy, will be combined with newer targeted therapies. This review introduces these new targeted therapies in the context of current treatment options for patients with GBM. It is hoped that this combined approach will overcome the current limitations in the treatment of patients with GBM and result in a better prognosis for these patients. *The Oncologist* 2006;11:152–164

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Glioblastoma Multiforme

The incidence of primary brain tumors has increased dramatically over the past several decades [1]. More than half of the 18,000 patients diagnosed with malignant primary brain tumors in the U.S. each year have glioblastoma multiforme (GBM), the most common primary brain tumor in adults [2]. Although GBM occurs in patients of all ages, the incidence is highest in the elderly, and GBM is slightly more common in whites and men [2, 3].

GBM is an anaplastic, highly cellular tumor with poorly differentiated, round, or pleomorphic cells, occasional multinucleated cells, nuclear atypia, anaplasia, endothelial proliferation, and pseudopalisading necrosis [3]. Signs and symptoms of GBM depend on the location, size, and rate of growth of the tumor and include headaches, seizures, focal neurologic deficits, and changes in mental status [2]. The World Health Organization classification system is used predominantly for naming astrocytomas, and in this system GBM can also be referred to as a grade IV astrocytoma [4].

Favorable prognostic factors include young age, good Karnofsky performance status (KPS) score, histology, absence of extensive necrosis, and a small residual tumor after surgical debulking [1, 2, 5, 6]. In the Brain Tumor Cooperative Group trials, 50% of patients aged <40 years survived for 18 months, compared with 10% of patients aged >60 years [2, 7]. Moreover, 34% of patients with KPS scores >70 were alive at 18 months, compared with 13% of patients with lower scores [2, 7].

Primary GBM develops de novo from glial cells, typically has a clinical history of <6 months, and is most common in older patients [8]. Secondary GBM develops over months or years from preexisting low-grade astrocytomas and predominantly affects younger patients [8]. The pathogenesis of GBM is most likely a multistep process that appears to involve several potential genetic alterations. Primary GBM tumors exhibit overexpression (>60% of cases) or amplification (>40% of cases) of the epidermal growth factor (EGF) gene (Fig. 1) [9–11]. The genetic alterations leading to these tumors also include loss of chromosome 10, amplification and overexpression of murine double minute 2 (MDM2), and deletion or mutation of the phosphatase and tensin homolog deleted from chromosome 10 (PTEN) gene [8]. In contrast to primary GBM, the development of secondary GBM is associated with inactivation of the tumor protein 53 (TP53) gene and overexpression of platelet-derived growth factor (PDGF) ligands and receptors [8, 9, 11]. This improved understanding of mechanisms of disease in GBM has led to advances in the use of existing agents and the development of new targeted therapies. These treatment options and their limitations are reviewed in this article.

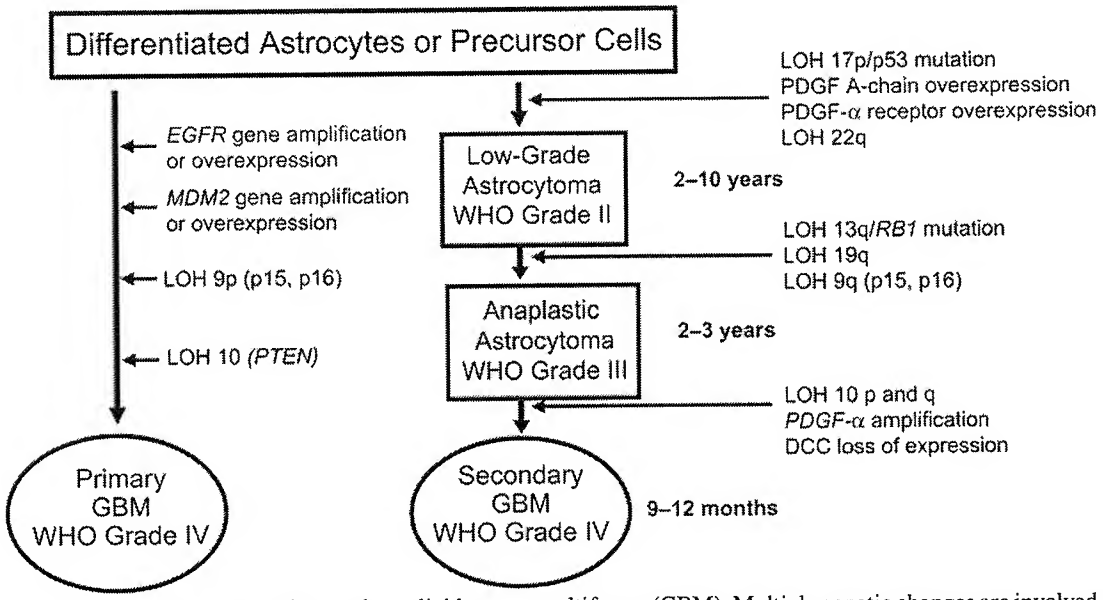

Figure 1. Formation of primary and secondary glioblastoma multiforme (GBM). Multiple genetic changes are involved in the development of primary and secondary glioblastomas. Controlling tumor growth will likely require the inhibition of multiple targets. Abbreviations: DCC, deleted in colorectal cancer; EGFR, epidermal growth factor receptor; LOH, loss of heterozygosity; MDM2, murine double minute 2; PDGF, platelet-derived growth factor; PTEN, phosphate and tensin homolog deleted on chromosome 10; *RB1*, retinoblastoma 1 gene; WHO, World Health Organization. Adapted from Tysnes BB, Mahesparan R. Biological mechanisms of glioma invasion and potential therapeutic targets. J Neurooncol 2001;53:129–147, with kind permission from Springer Science and Business Media, and with permission from Ohgaki H. Genetic pathways to glioblastomas. Neuropathology 2005;25:1–7, with kind permission from Blackwell Publishing.

Current Treatment Options for GBM

Despite modern treatments and diagnosis techniques, the median survival duration for patients with GBM is only 9–15 months, and the majority die within 2 years [2]. Although GBM is surgically incurable in the vast majority of patients, surgical techniques remain an important tool for the management of patients with GBM, and complete surgical resection continues to be the goal [1]. Regardless of degree of resection, adjuvant therapy—historically limited to radiotherapy (RT) and more recently expanded to include RT plus chemotherapy—is administered after surgery (all patients receive RT regardless of the extent of resection). In early randomized studies, significant increases in survival (14–36 weeks) were achieved in patients with high-grade gliomas with the administration of 50–60 Gy of whole-brain radiation following surgery [2, 7, 12]. Although adjuvant chemotherapy is also used in the treatment of GBM, until recent clinical trials, adjuvant chemotherapy had only demonstrated a moderate increase in survival in a large retrospective meta-analysis [1, 2, 13–15].

However, recent trials investigating temozolomide (Temodar®; Schering-Plough Corporation, Kenilworth, NJ) have demonstrated efficacy in patients with recurrent glioblastomas [16]. Moreover, temozolomide plus RT in newly diagnosed patients resulted in a significantly longer median survival time and significantly greater 2-year survival rate than RT alone [17]. Nonetheless, although this important study established a new therapeutic standard of care, the median progression-free survival and overall survival times achieved with temozolomide plus RT were only 6.9 and 14.6 months, respectively. Furthermore, clinical benefits associated with the addition of temozolomide has been shown to be significantly compromised in patients with tumors exhibiting increased activity of the DNA repair enzyme O^6-alkylguanine-DNA alkyltransferase [18, 19].

Despite clinical and technological advances in the understanding and treatment of brain tumors over the last three decades, the survival of patients with GBM has not notably improved. With the exception of the modest activity associated with temozolomide, there is no standard chemotherapy for patients with high-grade glioma, and resistance to chemotherapy is common [13]. Moreover, it is unknown whether further refinements in imaging, surgery, radiation, or standard chemotherapy regimens will have a meaningful impact on the outcome of this disease [2]. Therefore, research focused on the development of new targeted agents and approaches is needed.

Targeted Agents

Treatment of GBM often fails because the tumors are highly resistant to conventional cytotoxic chemotherapy and RT. However, knowledge of aberrant signaling pathways involved in GBM has elucidated new potential therapeutic targets (Fig. 2). Recent developments in targeted drug therapies may result in better treatment options for patients with GBM, and many of these agents are currently being tested in clinical trials (Table 1) [10].

Tyrosine Kinase Inhibitors

Proliferation and survival pathways are mainly regulated via growth factors and their respective receptors [20]. EGF has been implicated in supporting oncogenesis and progression of human solid tumors and is a promising target for anticancer therapy [21]. In fact, the EGF receptor (EGFR) is amplified in >40% and overexpressed in >60% of glioblastomas [9, 10]. Moreover, upregulation of EGFR is positively correlated with GBM malignancy, and EGFR signaling may play a role in radiation resistance [20]. Initial investigations of targeted molecular therapies in GBM have focused on the inhibition of tyrosine kinases and associated growth factor pathways. Gefitinib (Iressa®; AstraZeneca Pharmaceuticals, Wilmington, DE) is a selective small-molecule inhibitor of the EGFR [10, 20]. Although gefitinib is generally well tolerated, patients with GBM in initial clinical trials with gefitinib had minimal tumor response and no improvement in overall survival [10, 22]. In one phase II study, 13% of patients remained progression free for a minimum of 6 months in response to gefitinib monotherapy [22]. A phase I/II study conducted by the North American Brain Tumor Consortium (NABTC) demonstrated partial responses after previous RT in 5 of 38 patients with GBM enrolled in the phase II study [23].

Erlotinib (Tarceva®; OSI Pharmaceuticals, Inc., Melville, NY) is another small-molecule inhibitor of the EGFR that also inhibits the constitutively active mutant EGFRvIII found in approximately 40% of GBM cases [10, 20]. Although erlotinib has also been generally well tolerated, initial clinical trials have produced mixed results. In an early phase I study, treatment of patients with GBM with erlotinib, alone or in combination with temozolomide, resulted in 8 partial responses, and two patients with stable disease (response rate, 40%) [24]. In addition, in an ongoing phase II study in patients with recurrent GBM, an overall response rate of 25% was reported, with an additional 25% of patients experiencing stable disease [25]. However, in another phase II study, the median progression-free survival time was only 12 weeks in patients treated with erlotinib [26]. Therefore, the potential role for erlotinib in the treatment of patients with GBM remains to be determined. The activity of EGFR tyrosine kinase inhibitors is influenced by activating EGFR mutations in the kinase domain, which are observed in patients with

non-small cell lung cancer (NSCLC) but have not been observed yet in patients with GBM [27]. Furthermore, limitations imposed by the blood–brain barrier may have had an impact on the clinical activity of EGFR tyrosine kinase inhibitors to date.

Recent data suggest that detection of phosphorylated protein kinase B (Akt) in tumor specimens may predict lack of response to EGFR inhibitors [28]. Studies with dual tyrosine kinase inhibitors are also under way, which include early clinical trials on lapatinib (GW-572016; GlaxoSmith-Kline, Philadelphia), an EGFR and ErbB-2 inhibitor; and AEE788 (Novartis Pharmaceuticals Corporation, East Hanover, NJ), an EGFR and vascular endothelial growth factor (VEGF) receptor (VEGFR) inhibitor [10]. Lapatinib has exhibited preliminary evidence of biologic and clinical activity in ErbB-overexpressing tumors [29], and AEE788 has antiproliferative and antiangiogenic activity in vitro and in vivo and is currently in phase I clinical trials [30].

In addition to the upregulation of EGFR signaling, upregulation of the PDGF receptor (PDGFR) pathway is also found in GBM [20]. Imatinib mesylate (Gleevec®; Novartis Pharmaceuticals Corporation) is a potent small-molecule inhibitor of the Bcr-Abl receptor tyrosine kinase that has inhibitory effects on the PDGFR. Despite poor penetra-

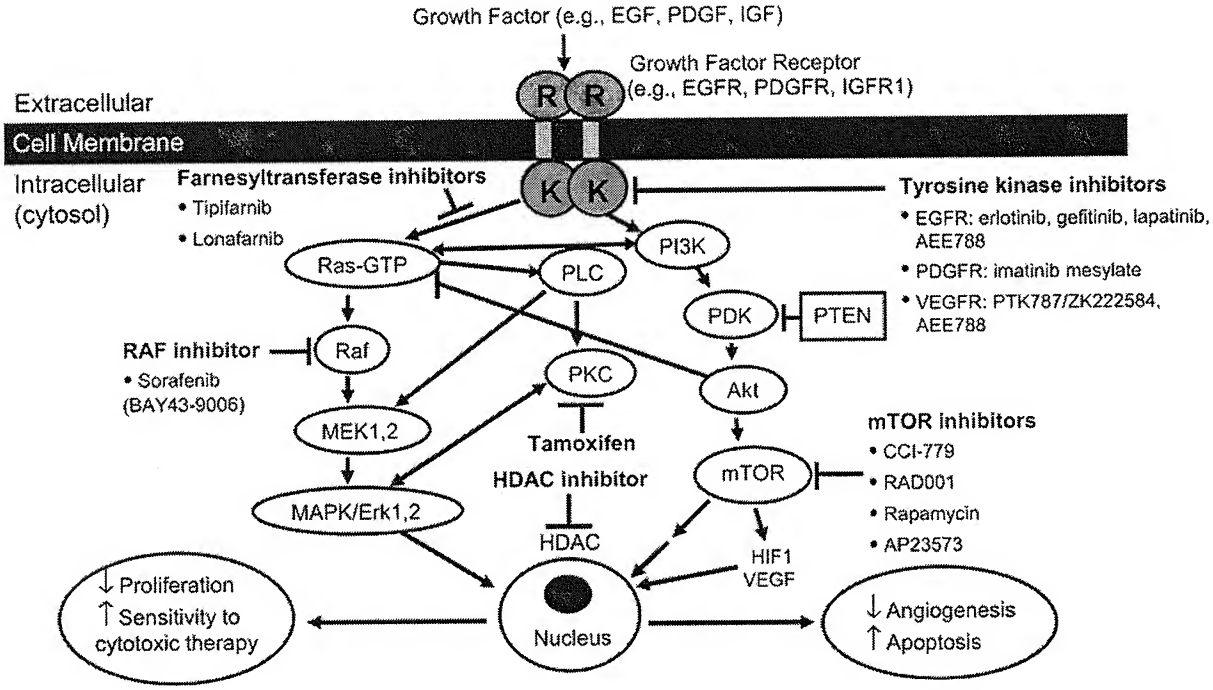

Figure 2. Therapeutic opportunities in growth factor receptor signaling pathways in glioblastoma multiforme. The tyrosine kinase activity of growth factor receptors is stimulated upon the binding of their cognate growth factors, which results in the stimulation of multiple downstream signaling cascades. These signaling pathways are important for a wide range of cellular functions, including protein synthesis, transcription, angiogenesis, regulation of the cell cycle, cell proliferation, and survival. Many components of these intracellular signaling pathways are potential therapeutic targets for developing new treatments against malignant gliomas, which are associated with poor prognosis in spite of all the therapeutic options currently available. Novel therapies targeting mechanisms involved in cell cycle dysregulation, evasion of apoptosis, angiogenesis, and escape from immune regulation offer promise for improving the prognosis of patients with malignant gliomas. Most of these novel agents have so far proven to be well tolerated but with limited efficacy as single agents. The combination of different targeted agents or the combination of targeted agents with conventional chemotherapy and radiotherapy may improve the antitumor efficacy of new targeted agents. Abbreviations: EGF, epidermal growth factor; EGFR, EGF receptor; ERK, extracellular signal–regulated kinase; GTP, guanadine triphosphate; HDAC, histone deacetylase; HIF1, hypoxia-inducible factor 1; IGF, insulin-like growth factor; IGFR1, IGF receptor 1; K, tyrosine kinase domain; MAPK, mitogen-activated protein kinase; MEK, MAPK/ERK kinase; mTOR, mammalian target of rapamycin; PDGF, platelet-derived growth factor; PDGFR, PDGF receptor; PDK, 3-phosphoinositide-dependent protein kinase; PI3K, phosphoinositol 3-kinase; PKC, protein kinase C; PLC, phospholipase; PTEN, phosphatase and tensin homolog deleted on chromosome 10; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor. Adapted from Kesari S, Ramakrishna N, Sauvageot C et al. Targeted molecular therapy of malignant gliomas. Curr Neurol Neurosci Rep 2005;5:186–197, with permission from Current Science, Philadelphia, and with permission from Jendrossek V, Belka C, Bamberg M. Novel chemotherapeutic agents for the treatment of glioblastoma multiforme. Expert Opin Investig Drugs 2003;12:1899–1924.

Table 1. Summary of targeted therapies for malignant glioma

$\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrin inhibitor
- Cilengitide

EGFR inhibitors
- Gefitinib
- Erlotinib
- Lapatinib(EGFR and ErbB-2 inhibitor)
- AEE788 (EGFR and VEGFR inhibitor)
- ZD6474 (VEGFR and EGFR inhibitor)
- EKB569
- Cetuximab (anti-EGFR monoclonal antibody)

Histone deacetylase inhibitors
- Depsipeptide (FK228)
- Suberoylanilide hydroxamic acid (SAHA)

Farnesyltransferase inhibitors
- Tipifarnib
- Lonafarnib

mTOR inhibitors
- Temsirolimus
- Everolimus
- Sirolimus
- AP23573

PDGFR inhibitors
- Imatinib mesylate
- PTK787 (PDGFR, VEGFR inhibitor)
- SU011248 (PDGFR, VEGFR, c-Kit inhibitor)
- Raf kinase inhibitor
- Sorafenib (VEGFR, PDGFR, and Raf kinase inhibitor)

Hsp-90 inhibitor
- 17-AAG (17-allylamino-geldanamycin)

VEGFR inhibitors
- Valatanib (PTK787) (PDGFR and VEGFR inhibitor)
- Sorafenib (VEGFR, PDGFR, and Raf kinase inhibitor)
- Sonitinib (PDGFR, c-Kit, and VEGFR inhibitor)
- AEE788
- AZD2171
- ZD6474 (VEGFR and EGFR inhibitor)

PKC inhibitors
- Tamoxifen
- Enzastaurin (PKC-ß2 inhibitor)

Proteasome inhibitor
- Bortezomib

Abbreviations: EGF, epidermal growth factor; EGFR, EGF receptor; hsp-90, heat shock protein 90; mTOR, mammalian target of rapamycin; PDGFR, platelet-derived growth factor receptor; PKC, protein kinase C; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.
From Kesari S, Ramakrishna N, Sauvageot C et al. Targeted molecular therapy of malignant gliomas. Curr Neurol Neurosci Rep 2005;5:186–197, with permission of Current Science, Philadelphia.

tion across the blood–brain barrier, imatinib mesylate has been associated with modest activity in patients with recurrent GBM in phase II trials [31, 32]. Additionally, imatinib mesylate significantly enhanced the cytotoxic effect of ionizing radiation in a human glioblastoma cell line [33]. Additional studies will determine whether imatinib mesylate has a role in the treatment of GBM. CP-673,451 (Pfizer Pharmaceuticals, New York), another inhibitor of the PDGFR pathway, potently inhibited PDGFR-β in an ex vivo glioblastoma tumor model [34]. Other potential tyrosine kinase targets include the inhibition of Ras/mitogen-activated protein kinase (MAPK) and phosphoinositide 3 kinase (PI3K)/Akt pathways, farnesyltransferase, rapamycin, histone deacetylation, insulin-like growth factor receptor (IGFR), cell cycle components, transforming growth factor beta (TGF-β), and heat shock protein 90 (hsp-90) (Table 1) [10]. Further development of tyrosine kinase inhibitors for GBM patients should include study designs that incorporate intratumoral pharmacodynamic assessment of specific target inhibition. Validation of suppression of target signaling is of particular importance for brain tumors, given the inherent difficulties associated with delivery of therapeutics into the central nervous system (CNS).

Angiogenesis Inhibitors

The growth and survival of GBM are dependent on an adequate blood supply, and not surprisingly, malignant gliomas are highly vascularized [10]. The formation of new blood vessels is coordinated by the complex interaction of many angiogenic factors, including VEGF, basic fibroblast growth factor (bFGF), and PDGF [10]. Therefore, targeting factors and pathways implicated in angiogenesis may represent potential approaches to the treatment of this disease.

Because VEGF represents a major stimulatory factor for the initiation of angiogenesis, the inhibition of VEGFRs is a promising treatment for malignant gliomas [10, 20]. PTK787/ZK 222584 (Novartis Pharmaceuticals Corporation and Schering AG Corporation), a VEGFR tyrosine kinase inhibitor, decreases glioma growth and vascularization in vivo and is currently being investigated in phase I/II trials alone or in combination with lomustine or temozolomide in patients with GBM [10, 35].

Other VEGFR inhibitors, including ZD6474 (Zactima™; AstraZeneca Pharmaceuticals) and CEP-7055 (sanofi-aventis, Bridgewater, NJ), have produced significant growth inhibition of glioblastoma xenografts in nude mice [10]. Clinical trials of these and other VEGFR inhibitors, such as sorafenib (BAY 43-9006; Bayer Pharmaceuticals Corporation, West Haven, CT, and Onyx Pharmaceuticals, Emeryville, CA) and AZD2171 (AstraZeneca Pharmaceuticals), are ongoing or being planned [10, 36].

In recent trials, monotherapy with thalidomide (Thalomid®; Celgene Corporation, Warren, NJ) has been investigated for the treatment of GBM because of its antiangiogenic effects. However, results suggest thalidomide alone has only moderate antitumor activity in patients with recurrent high-grade gliomas [20, 37]. Nonetheless, the combination of thalidomide and chemotherapy appears to be more active in patients with recurrent gliomas than either agent alone [20, 38]. The $\alpha_v\beta_3$ integrin inhibitor cilengitide (EMD 121974; EMD Pharmaceuticals, Durham, NC) induces apoptosis in brain tumor cells, and the protein kinase C (PKC) β2 inhibitor enzastaurin (LY317615; Eli Lilly and Company, Indianapolis) decreases VEGF levels in a mouse tumor model [39, 40]. Phase II trials in recurrent gliomas are under way for both of these agents [10]. Furthermore, metalloproteinase inhibitors, including SI-27 (Shionogi and Company Ltd., Osaka, Japan) and batimastat (British Biotech Pharmaceuticals, Ltd., Oxford, UK), inhibit angiogenesis invasion in vivo and have therapeutic potential for the treatment of GBM [10, 41]. Other angiogenic inhibitors of interest include cyclooxygenase 2 (COX-2) inhibitors, angiostatin, atrasentan (Abbott Laboratories, Abbott Park, IL), and lenalidomide (Revlimid®; Celgene Corporation) [10, 20, 42–44].

A new approach for delivering antiangiogenic agents to gliomas uses naked plasmid DNA targeted to brain tumors via intra-arterial injection [45]. The intra-arterial delivery of the gene for endostatin, a suppressor of angiogenesis, was recently investigated in a rat gliosarcoma model. Administration of the endostatin gene resulted in an 80% tumor volume reduction, and survival time was up to 47% longer [45].

To achieve the greatest therapeutic benefit from antiangiogenic agents, it will be important to determine the most effective combinations of therapies and drugs. Agents that target multiple receptors, including sorafenib, valatinib (PTK787/ZK222584), sunitinib (SU011248) (Pfizer Pharmaceuticals, New York), ZD6474 (zactima) and AEE788, allow a multipronged attack against vascularization (Table 1) [10, 46]. Ultimately, the most effective treatment strategies may be tailored to the molecular phenotype of a patient's tumor and include chemotherapy in combination with cytostatic agents.

Bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA), a recombinant, humanized monoclonal antibody targeting VEGF, has been recently approved for use in colorectal carcinoma based on a significant survival benefit observed following its addition to fluorouracil-based chemotherapy [47]. Similarly, Stark-Vance recently reported that, among 21 patients with recurrent malignant glioma treated with bevacizumab plus irinotecan (Camptosar®; Pfizer Pharmaceuticals), one patient achieved a complete response, eight achieved partial responses, and 11 achieved stable disease [48]. Overall, the regimen was reported as well tolerated, although two deaths occurred on treatment, including one patient with an intracranial hemorrhage and one patient with bowel perforation. A formal, single-arm phase II study of bevacizumab plus irinotecan is being performed at the Preston Robert Tisch Brain Tumor Center at Duke University Medical Center for patients with recurrent malignant glioma. Preliminary analyses of results of this trial reveal that this regimen is well tolerated among malignant glioma patients and is associated with a highly exciting rate of radiographic response. Further investigation of the regimen of bevacizumab plus irinotecan is planned.

Other Noncytotoxic Targeted Therapies

Inhibitors of Ras/MAPK and PI3K/Akt Pathways

Activation of a variety of growth-factor receptor pathways are thought to be involved in the development of malignant gliomas. Identifying and targeting common downstream mediators of growth-factor signaling, such as the Ras/MAPK and PI3K/Akt pathways, may yield additional potential therapeutic options. Farnesyltransferase is involved with signal transduction in the Ras pathway, and two farnesyltransferase inhibitors, tipifarnib (Zarnestra™; Ortho Biotech Products, L.P., Bridgewater, NJ) and lonafarnib (Sarasar™; Schering-Plough Corporation), have been evaluated in clinical trials in patients with malignant gliomas (Table 1) [10, 49]. Tipifarnib had modest activity in gliomas as a single agent in phase I/II trials, and combined trials with RT or temozolomide are under way [10, 50]. Although gastrointestinal toxicities were reported, positive clinical activity was observed in pancreatic and NSCLC in phase I/II studies of lonafarnib [51].

The PI3K/Akt pathway is activated through a sequence of events involving several growth-factor receptors, including EGFR and PDGFR [10]. The PTEN tumor suppressor gene, which is inactivated in 40%–50% of GBM cases, usually inhibits the PI3K/Akt pathway. Greater PI3K activity has been associated with greater resistance to RT [52]. Therefore, inhibitors of the PI3K/Akt pathway may be potential therapeutic agents for GBM. Several inhibitors of the mammalian target of rapamycin (mTOR)—a downstream target of PI3K signaling—are being investigated in clinical trials [10, 53, 54]. These agents include sirolimus (rapamycin, Rapamune®; Wyeth, Madison, NJ), temsirolimus (CCI-779; Wyeth), everolimus (Certican®; Novartis Pharmaceuticals Corporation), and AP23573 (ARIAD Pharmaceuticals, Inc., Cambridge, MA), all of which inhibit glioblastoma cell proliferation in culture and intracerebral xenografts. Temsiro-

limus demonstrated modest activity in recurrent gliomas in recent phase I/II studies [55, 56]. LY294002, an inhibitor of PI3K, sensitized a mutant glioma cell line to doses of clinically relevant radiation [52].

Inhibitors of Proteasomes and Histone Deacetylases

The ubiquitin/proteasome system is the main post-transcriptional degradation mechanism of proteins involved in the cell cycle, DNA transcription and repair, apoptosis, angiogenesis, and cell growth [57]. Therefore, the development of drugs that target this system is a potential new anticancer strategy. Indeed, bortezomib (Velcade®; Millennium Pharmaceuticals, Inc., Cambridge, MA), a proteasome inhibitor, induces apoptosis in human GBM cell lines and primary GBM explants and is currently in phase I trials in patients with recurrent or progressive gliomas [57, 58].

There is evidence that histone acetyltransferase activity is altered in malignant gliomas [10]. Clinical trials of several histone deacetylase inhibitors, including valproic acid, depsipeptide, and suberoylanilide hydroxamic acid (SAHA), are under way or planned [59]. Other potential targets for therapy of malignant gliomas include poly (ADP-ribose) polymerase (PARP), nuclear factor kappa B (NFκB), IGFR, Raf, MAPK/extracellular signal–regulated kinase (ERK) kinase (MEK), Akt, cell cycle components, TGF-β, aurora kinases, and hsp-90 [10, 60–62].

Intratumoral Therapy

Approaches that directly target the tumor increase the exposure of tumor cells to the drug and reduce the probability of systemic complications. Cancer cells frequently express different cell surface proteins than their noncancerous counterparts [63]. Therefore, regional delivery of monoclonal antibodies to the tumor is an area of ongoing research [54]. Indeed, a category of monoclonal antibodies raised against the EGFR recognizes tumors with EGFR amplification/overexpression but not normal tissues or tumors with native EGFR levels [64]. Moreover, recent studies using radiolabeled monoclonal antibodies directed at tenascin or EGFR show that a survival benefit in patients with gliomas may be possible with intratumoral immunotherapy [10, 65]. In addition, monoclonal antibodies can be armed with toxins to target tumors [63]. For example, an antibody generated to a mutant EGFR that is fused to *Pseudomonas* exotoxin A generates an immunotoxin with good affinity, cytotoxicity, and stability [66].

Toxins

Toxins have also been investigated as potential intratumoral therapies. Toxins are generally delivered by convection-enhanced delivery (CED). CED establishes a pressure gradient during interstitial infusion into the brain that allows greater administration of drugs through slow infusion of the drug over a period of several days through stereotactically placed catheters [54, 67]. New methods of drug delivery into the brain using implantable drug-releasing biodegradable microspheres have also been introduced [68]. ^{131}I-TM-601 is a radiolabeled peptide derived from scorpion venom that binds to chloride channels in gliomas, and, although it is well tolerated, no efficacy data are currently available [10]. Transferrin-CRM107, a conjugate of the diphtheria toxin linked to transferrin, has produced tumor response in phase I and II trials without severe toxicity [69].

Two other examples of targeted cytotoxins using *Pseudomonas* exotoxin are interleukin (IL)-13 fused with *Pseudomonas* exotoxin (IL13-PE38QQR) and TGF-β fused with *Pseudomonas* exotoxin (TP-38). IL13-PE38QQR was safe and produced responses in patients with malignant gliomas in early phase I/II studies [70, 71]. TP-38 targets glioma cells expressing the EGFR [72]. TP-38 was well tolerated, and 20% of patients in a phase I trial had radiographic responses [72]. Similarly, DAB389EGF targets EGFR-overexpressing cells; therefore, clinical trials are planned for the fusion of EGF and diphtheria toxin [67, 73].

Immunotherapy

Cytokines represent another potential therapeutic target for many tumor types (e.g., glioma) because of their immunomodulating effects [41]. TGF-β2, a cytokine that promotes glioma invasion, angiogenesis, and immunosuppression, is a potential target of GBM therapy [74]. SB-431542 (Sigma-Aldrich, St. Louis), a novel small-molecule inhibitor of the TGF-βR, prevented glioma growth in preclinical trials [74]. Additionally, AP12009 (Antisense Pharma, Regensburg, Germany), a TGF-β2 antisense oligonucleotide, produced some antitumor activity and was safe in early clinical trials [10, 74]. Use of IL-4 to target tumors may represent the most clinically viable use of cytokines. Six of nine patients who received IL-4 cytotoxin (IL-4 fused to *Pseudomonas* exotoxin) had necrosis of their tumors without damage to surrounding tissues [41]. Because of these promising findings, phase II/III trials are under way.

Combination Regimens

Because GBM is an infiltrative disease that is often resistant to treatment, a combination of treatment modalities is likely necessary to achieve the most therapeutic benefit. Indeed, in recent trials, temozolomide plus RT after standard surgery and in newly diagnosed patients without surgery resulted in a significantly longer median survival time and significantly greater 2-year survival rate than with

RT alone in patients with GBM [17, 38]. This combination of surgery, chemotherapy, and RT is likely to become the new standard of care until newer, more effective agents are developed. In addition, the combination of two or more antitumor agents that have different targets may also become a viable treatment option for GBM. For example, combining patupilone (Novartis Pharmaceuticals Corporation), a microtubule-stabilizing agent; and imatinib mesylate, a tyrosine kinase inhibitor, was associated with a greater antitumor effect than with either therapy alone in a rat glioma model [75]. Moreover, in phase II trials, the combination of paclitaxel (Taxol®; Bristol-Myers Squibb, Princeton, NJ), a microtubule-stabilizing agent; topotecan (Hycamtin®; GlaxoSmithKline), a topoisomerase I inhibitor; and filgrastim (Neupogen®; Amgen Inc., Thousand Oaks, CA) support has resulted in modest activity in adults with recurrent or refractory GBM and anaplastic astrocytoma [76]. Unfortunately, despite filgrastim support, hematologic toxicity was common with this regimen [76].

In addition, many clinical trials that attempt to build on the clinical activity recently described for temozolomide in patients with newly diagnosed GBM are either under way or soon to be initiated [17]. For example, the regimen of temozolomide plus irinotecan has been associated with encouraging activity [77].

Because the expression or amplification of various receptors is altered in GBM, agents targeting multiple receptors, such as sorafenib (VEGFR, PDGFR, and Raf kinase inhibitor), PTK787/ZK222584 (VEGFR and PDGFR inhibitor), SU011248 (VEGFR, PDGFR, and c-Kit inhibitor), and AEE788 (VEGFR and EGFR inhibitor), are potentially useful therapeutic combinations. Moreover, combinations of receptor inhibitors with inhibitors of downstream signaling pathways and targets also hold promise for the treatment of GBM. For example, the combination of AEE788, an inhibitor of EGF and VEGFR, and RAD001, an mTOR inhibitor, resulted in more tumor growth inhibition in a mouse glioma model than monotherapy [78]. Kinase inhibitors that target downstream effectors common to multiple upstream receptors may prove to be efficacious in heterogeneous GBM. Furthermore, the addition of antiangiogenic and intratumoral agents to the overall treatment strategy may provide additional options for the successful treatment of GBM. The combination of endostatin (a direct angiogenesis inhibitor) and SU5416 (Pfizer Pharmaceuticals), a VEGFR inhibitor, has been reported to reduce tumor growth in glioma xenograft models, compared with treatment with either therapy alone [79].

The combination of targeted molecular therapy and RT or chemotherapy is also a promising therapeutic option. Overactivity of the EGFR pathway is associated with resistance to treatment with RT and chemotherapy [10, 80]. Therefore, combining targeted EGFR therapy with RT or chemotherapy may increase the effectiveness of treatment. Indeed, the combination of an EGFR antibody with irradiation in patients with head and neck cancer resulted in superior tumor control and survival compared with irradiation alone [81]. However, acute skin reactions were greater in the experimental arm of this study [81].

Thalidomide has also been successfully combined with cytotoxic agents. For example, patients with recurrent GBM treated with a combination of thalidomide and carmustine (BCNU®; Bristol-Myers Squibb) had an objective response rate of 24%, which compared favorably with carmustine treatment alone [38]. Moreover, the combination of thalidomide and temozolomide in patients with GBM was more effective than thalidomide alone with respect to survival, stable disease, and response [82].

Increased expression of COX-2 is associated with angiogenesis and resistance to many cytotoxic chemotherapy drugs [10, 83]. Celecoxib (Celebrex®; Pfizer Pharmaceuticals), a COX-2 inhibitor, enhanced antitumor activity of chemotherapy drugs in vitro and in vivo in prostate tumor cells [83] and has been effectively combined with chemotherapy for patients with recurrent malignant glioma [84]. Moreover, rofecoxib (Vioxx®; Merck & Co., Inc., Whitehouse Station, NJ), another COX-2 inhibitor, in combination with chemotherapy has been shown to be safe in patients with GBM [85].

An Update from the 2005 Annual Meeting of the American Society of Clinical Oncology

A number of communications regarding the development of targeted agents for the treatment of GBM were presented at the 2005 Annual Meeting of the American Society for Clinical Oncology (ASCO). One of the most interesting reports was a phase II trial investigating enzastaurin for the treatment of patients with recurrent high-grade gliomas [86]. Enzastaurin is a potent and selective inhibitor of PKC-β, which seems to be of importance in the VEGF signaling cascade; this is particularly important in the context of GBM, in which VEGF appears to be the predominant angiogenic factor. The exposure to enzastaurin was significantly lower in patients treated with enzyme-inducing anti-epileptic drugs (EIADs). Eighty-seven patients were evaluable for response, and 22% of the patients with GBM had objective radiographic responses. Five percent of patients had stable disease, and the overall progression-free survival duration for responders and patients with stable disease was approximately 5 months. One of the main toxicities reported was thrombocytopenia (16% of patients experienced some form of it, and

3% of patients had grade 3–4). Seven patients had intratumoral bleeds, but no deaths occurred. Of these seven patients, six had progressive disease on enzastaurin at the time of the bleed, and one patient was responding. There is a potential association between treatment of fully anticoagulated patients with GBM with enzastaurin and intratumoral hemorrhage.

Imatinib mesylate is another targeted agent for which data were presented at the 2005 ASCO annual meeting. A multicenter phase II study investigated imatinib mesylate in patients with recurrent anaplastic oligodendroglioma (AOD)/mixed oligoastrocytoma (MOA) and anaplastic astrocytoma (AA)/low-grade astrocytoma (LGA). Use of imatinib mesylate as a single agent displayed a good safety profile, but limited activity, in patients with AOD/MOA and AA/LGA [87].

The safety and efficacy of the combination of imatinib mesylate and hydroxyurea was investigated to test the synergy of these agents in patients with recurrent refractory GBM. In one study, the rate of complete response and partial response was 20%, while the clinical benefit rate, including stable disease, was 57%. The progression-free survival rate at 2 years was 16% [88]. In addition, a phase II study to evaluate the activity of imatinib mesylate combined with hydroxyurea for the treatment of patients with recurrent malignant glioma was conducted by Friedman et al. [89]. Nine percent of GBM patients achieved radiographic responses, while 35% achieved stable disease. The median progression-free survival time for patients with recurrent AA/AOD was 10.9 weeks, and for those with GBM, it was 14.4 weeks. The progression-free survival rate at 6 months was 26.3%. Results for the rate of radiographic response, the median progression-free survival time, and the 6-month progression-free survival rate compare favorably with the results seen in the study of temozolomide in first relapse. The greater activity of imatinib mesylate when administered in combinations with hydroxyurea may be due partly to PDGFR inhibition by imatinib mesylate and the antiangiogenic effect of continuous hydroxyurea dosing [88, 89].

The maximum-tolerated dose and dose-limiting toxicity of imatinib mesylate in combination with temozolomide was evaluated in a phase I dose-escalation study in patients with malignant glioma [90]. The maximum-tolerated dose has yet to be defined, and to date no dose-limiting toxicity has been observed.

Erlotinib is another targeted agent for which data were reported, including an update of a phase II study presented at the ASCO 2004 annual meeting regarding the use of erlotinib for patients with GBM in first relapse [91]. Of 48 patients, the response rate was 8.4%, and stable disease was observed in 37.5% of patients. The 6-month progression-free survival rate was 17%, and the median survival time was 10 months. Molecular analyses showed a slight trend toward better outcome with EGFR expression, but the sample size was too small for the difference to be significant.

A phase I trial of erlotinib with RT in patients with GBM determined the toxicity and maximum-tolerated dose [92]. The median time to progression was 161 days, and the median survival time was 386 days. Thirteen patients were evaluable for best objective response (nine had stable disease, one had no evidence of disease, and three had early progression). Preliminary data suggest that the concomitant administration of erlotinib plus RT is well tolerated.

The combination of erlotinib with temozolomide and concurrent RT in a phase II study enrolling patients with newly diagnosed GBM was presented [93]. The best response evaluated was stable disease (10.5 months, 7 months, and 3.5+ months' duration). No grade 4 toxicities were observed, and grade 3 adverse events included neutropenia and lymphopenia. These observations suggest that the combination of erlotinib with RT and temozolomide appears to be feasible and, in general, well tolerated.

Treatment with gefitinib for adult patients with progressive high-grade gliomas (HGGs) was investigated in an open-label, single-arm, phase II study by the Gruppo Italiano Cooperativo di Neuro-Oncologia (GICNO) [94]. Adult patients with histologically confirmed high-grade gliomas recurring after first-line chemotherapy were enrolled. Of 16 patients with GBM, one patient had an unconfirmed partial response, five patients had confirmed stable disease, and three patients had unconfirmed stable disease. Adverse events included grade 3 diarrhea and neutropenia and grade 4 acute pulmonary edema, pulmonary thromboembolism, and CNS hemorrhage. In the GBM subgroup of patients, the disease-control rate was 12.5%, and the median time to progression was 60 days. Both at 6 and 12 months, the rate of progression-free survival was 12.5%. The median overall survival duration was 172 days, and the rates of overall survival at 6 and 12 months were 50% and 14.3%, respectively. These results suggest that gefitinib may be active as a second-line treatment in patients with HGG.

Data from a phase I trial of gefitinib in combination with rapamycin for the treatment of patients with recurrent malignant glioma were also presented [95]. Another phase I study evaluated the safety of escalating doses of atrasentan in adults with recurrent malignant glioma [96]. Atrasentan is a highly potent and selective endothelin A receptor agonist that may inhibit cell proliferation by blocking the endothelin A receptor that regulates the angiogenesis involved in glioma growth. The maximum-tolerated dose was determined to be 70 mg per day.

Twenty-three patients were evaluable for toxicity; the most common adverse events were rhinitis, headache, and peripheral edema; myelosuppression was not observed. One patient had a partial response, one patient had an unconfirmed partial response, and four patients had stable disease before progressing. The median survival time was 6 months, and the median progression-free survival time was 1.5 months. The observed 6-month progression-free survival rate was comparable with historical data.

Data from the N997B phase II trial of temsirolimus in patients with GBM and with one prior chemotherapy regimen for progressive disease or less were reported [97]. Temsirolimus was shown to be well tolerated in patients with recurrent GBM. Radiographic response in patients treated with temsirolimus was associated with a significantly longer progression-free survival time. Results suggested that the development of grade ≥2 hyperlipidemia appears to be a surrogate marker of radiographic improvement. High levels of phosphorylated p70s6 kinase, as determined by immunohistochemistry in baseline tumor samples, appear to be able to predict which patients are most likely to benefit from treatment.

Final results of a phase I/II study of IL13-PE38QQR administered intratumorally and/or peritumorally via CED in patients undergoing tumor resection for recurrent malignant glioma showed that, for patients with GBM who are undergoing tumor resection, CED of IL13-PE38QQR is associated with a favorable risk-to-benefit profile [98].

Conclusions and Future Directions

Infiltration of tumor cells into the surrounding brain may be responsible for the refractory nature of GBM to treatment [99]. Indeed, surgical treatments are only palliative in nature and not curative. Moreover, the blood–brain barrier represents a significant obstacle for most antiglioma drugs. For example, the delivery of large-molecular-weight polar compounds, such as proteins, has proven to be especially challenging. In addition, the brain is highly sensitive to cytotoxic treatments, and venous thromboembolism commonly affects patients receiving treatment for cerebral tumors [100]. The frequency of spontaneous intracerebral hematomas in patients with intracranial neoplasms in a recent study was 2%, and 30% of those were related to GBM [101].

Another challenge for the successful treatment of GBM is the diversity of cell types and mutations in the tumor. These tumors are composed of highly heterogeneous cell populations that are often characterized by high chemoresistance [20]. Furthermore, because a variety of genes may be mutated or overexpressed in different areas of the tumors, no one treatment is likely to destroy the tumor. Although significant progress has been made, further elucidation of signaling pathways responsible for the malignant phenotype of GBM will represent a significant advance in the field. Once tumors can be more accurately classified by mutations, treatment regimens can be tailored to individual tumors. It is likely that the most effective treatments will combine traditional interventions such as surgery, irradiation, and chemotherapy with the newer targeted therapies.

Development of DNA- and RNA-based therapies represents a future direction for GBM therapy. Although the use of gene therapy is still in the experimental stages, it is a promising new area of research. Theoretically, gene therapy strategies can be designed on the basis of unique cytogenic and molecular characteristics of the tumor and can improve the selectivity and safety of treatment [102]. Similarly, antisense therapy is a promising new treatment strategy that is currently under investigation. Several genes, including *TGF-β*, *bFGF*, *EGFR-1*, *VEGF*, telomerase, topoisomerase II β subunit, PKC-β, and microtubule-associated protein 1A have been targeted by antisense technology in glioma cells [103].

Therapeutic vaccination of patients with cancer also represents an encouraging experimental approach to treating malignant gliomas [103]. Antigen-presenting dendritic cells are designed to potently stimulate antitumor T-cell responses that in turn destroy the tumor [104]. A recent phase I study demonstrated the ability of a tumor lysate-pulsed dendritic cell vaccine to generate antigen-specific cytotoxicity in patients with GBM and anaplastic astrocytoma [104].

In summary, recent therapeutic approaches are based on a greater understanding of the molecular and cellular biology of GBM. Some of the new cytostatic and noncytotoxic targeted agents currently under investigation may eventually add to the armamentarium of agents that can be used in combination with surgery, RT, and conventional cytotoxic agents for improved treatment of patients with GBM.

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Disclosure of Potential Conflicts of Interest

Patrick Wen and David Reardon have acted as a consultant for Schering-Plough and Novartis. David Reardon indicated a financial interest.

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